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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,626	PRATT ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☒ Claim(s) *19, 21,25, and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are pending.

Drawings

The drawings are objected to because the text in Figure 2 is difficult to read. The Examiner respectfully suggests using a different font and/or font size for the text in Figure 2. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, **or to a publication is improper.** On page 9 of

the specification, Applicant stated the incorporation by reference of all patents and references cited therein (see relevant journal citations on pages 5, 6, 10, 16, 24-31, and 38-40). This application refers to two U.S. patents which themselves incorporate essential material by reference, this is improper:

> **"In any application, which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application." See MPEP § 608.01 (p).**

Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The disclosure is objected to because of the following informalities: on page 32, line 29 the word "Chloride" following "methylene" should be spelled with a lower case 'c'; p 39, line 21 the chemical name "Chloral Hydrate" should be spelled with all lower case letters (a chemical name is only capitalized when it occurs at the beginning of a sentence); and on p 39, line 27 a space should be inserted between --"2.0"-- and --"mm"--.

Appropriate correction is required.

Claims 19 and 25 are objected to because of the following informalities: a comma is missing between the words --"medications"—and --"enzymes"-- between lines 5 and 6 of said claims. Appropriate correction is required.

Claims 21 and 28 are objected to because of the following informalities: the term "antibiotic delivery" has been included erroneously in a list of central nervous system disorders. Antibiotic delivery is not a disorder. Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademarks LUPRON DEPOT® (p 15, line 29), LIBRAFIL® 1944 (p 30, line 11), SPAN® 85 (p 32, line 2), GELFOAM® (p 33, line 30), and IMAGE PRO-PLUS® (p 35, line 30) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 13-16, 19-21, 25, 26, 28, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-15 recite the limitation "said ratio" in line 1 of said claims. There is insufficient antecedent basis for this limitation in the claim.

The term "cellulose derivatives" in claims 16 and 29 is considered indefinite, because it would be unclear to a person of ordinary skill in the art whether this term only encompassed compounds resulting from the non-destructive chemical modification of cellulose or if it also encompasses those molecules resulting from the chemical degradation of cellulose, such as monosaccharides. A skilled artisan would not be able to ascertain the metes and bounds of the term "cellulose derivatives."

The phrase "other types of neurological and psychiatric illnesses" in claims 21 and 28 is considered indefinite because it does not clearly delineate the metes and bounds of the claimed scope.

The term "non-steroidal products" in claims 20 and 26 is considered indefinite, because the scope of this term is unclear. It is uncertain whether Applicant intended the term "non-steroidal products" to refer solely to a certain class of compounds or if Applicant intended to include any product that lacked a steroidal structure, including, for example water, ethanol, nitrous oxide, or even wound-healing glass powders.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required

feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims (a) 19 and 25 and (b) 20 and 26 recite the broad recitation (a) living cells and (b) hormones and immunomodulators and the claim also recites (a) bone marrow cells or fetal neural tissue or stem cells and (b) (estrogens and anti-estrogens) and (immunostimulators and immunosuppressive), which is the narrower statement of the range/limitation, respectively.

Regarding claims 19 and 25, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the procedure required to contact a central nervous system tissue. The step of "contacting a central nervous system tissue" could entail the systemic administration of a therapeutic agent (i.e. it eventually will contact CNS tissue) as well as the intrathecal administration of a therapeutic agent. These two possibilities are significantly different from each other, therefore a person of ordinary skill in the art would not be able to determine which steps were encompassed by Applicant's method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Patton et al. (U.S. Patent No. 5,814,607).

Applicant's claims are drawn to biocompatible compositions comprising a therapeutic agent, a polymer, and a buoyancy agent (claim 1); wherein the polymer is biodegradable (claim 2); wherein the composition is controllably buoyant within the cerebrospinal fluid (claim 3); and wherein the buoyancy agent is a hydrofluorocarbon (claim 9).

Regarding the term "buoyancy agent" the adjective "buoyancy" is being read as meaning "the capacity to be able or apt to keep afloat or rise to the top of a liquid or gas" based upon the definitions of the words "buoyancy" and "buoyant" on page 97 of the *Oxford Pocket American Dictionary of Current English* (Oxford University Press: New York, 2002.).

Patton discloses compositions comprising **dispersed parathyroid hormone (PTH) fragment** in a volume of gas to produce an aerosolized bolus (column 2, lines 64-67). The PTH fragment is a therapeutic agent and a biodegradable polymer (i.e. a polypeptide).

Patton discloses that for use in metered dose inhalers (MDI's) the PTH fragments will be dissolved or **suspended** in a suitable aerosol propellant, including **hydrofluorocarbons** (column 6, lines 10-17).

Patton discloses that for pulmonary or respiratory administration the PTH fragment will be co-administered with **vitamin D calcitonin** and/or **dietary calcium supplements**. Both vitamin D calcitonin and calcium supplements are therapeutic agents.

Patton does not explicitly describe the hydrofluorocarbons used as buoyancy agents; however, this is an inherent property of the hydrofluorocarbons, especially when the therapeutic agents are suspended. Applicant defines the term "controllably buoyant" as "a polymer composition comprising at least one buoyancy agent (specification, page 8)." Hydrofluorocarbons are buoyancy agents, per applicant's admission. Tetrafluoroethane, a known hydrofluorocarbon, has a density at 25 °C that is greater than 1.0063 g/cm^3 and hexafluropropane has a density at 0 °C greater than 1.0063 g/cm^3 (See e.g. CRC Handbook of Chemistry and Physics, p 3-306 and 3-306). Specific gravity is the ratio of the mass of a substance and the mass of an equal volume of water at 4 °C. Thus, one gram of tetrafluorethane would occupy a volume of approximately 0.8 ml and would have a specific gravity of approximately 1.25, because water has a density of approximately 1.0 g/ml at this temperature. Therefore, Patton discloses all of the limitations of claims 1-3, 5, and 9.

Claims 1-3, 5, 9, 16, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Pitt et al. (U.S. Patent No. 5,354,934).

Applicant's claims 1-3 and 9 have been described supra. Claims 16 and 20, further limit claims 2 and 1, respectfully. Claim 16 introduces the limitation into claim 1 that the biodegradable polymer is a naturally derived polymer selected from the group consisting of albumin, alginate, cellulose derivatives, collagen, fibrin, gelatin, and polysaccharides. Claim 20 further limits claim 1, by requiring that the therapeutic agent is a cancer agent selected from the group consisting of vinca alkaloids and other plant products, cytostatic drugs, cytotoxic drugs, hormones, alkylating agents, immunomodulators, hematological agents, non-steroidal products, radiopharmaceuticals, antibodies, antiandrogens, and epidermals.

Pitt discloses MDI **erythropoieten** (EPO) respirable suspension formulations comprising EPO, human serum **albumin**, **lactose** (a disaccharide), and a **hydrofluorocarbon** (column 8, lines 63-67 and column 9, lines 1-16). EPO, albumin, and lactose are polymers according to applicant's definition on page 4 of the specification: "polymer" refers to molecules formed from the chemical union of two or more repeating units. As discussed *supra* per Applicant's admission, hydrofluorocarbons are buoyancy agents and compositions comprising at least one buoyancy agent are "controllably buoyant." Tetrafluoroethane, a known hydrofluorocarbon, has a density (i.e. specific gravity) at 25 °C that is greater than 1.0063 g/cm^3 and hexafluropropane has a density at 0 °C greater than 1.0063 g/cm^3 (See e.g. CRC Handbook of Chemistry and Physics, p 3-306 and 3-306). Furthermore, hydrofluorocarbons are inherently buoyant, especially when used in suspension formulations. Therefore, Pitt meets all the limitations of claims 1-3, 5, 9, and 20.

Claims 1, 2, 10, 12, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Green et al. (U.S. Patent No. 5,814,666).

Applicant's claims 1, 2, and 5 have been described supra. Claim 10 is drawn to the composition of claim 1, wherein the buoyancy agent is a gas selected from the group consisting of nitrogen, argon, carbon dioxide, helium, and xenon. Claim 12 is drawn to a composition comprising a first polymer particle comprising a first therapeutic agent and a second polymer particle comprising a second therapeutic agent.

Green discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier, including liposomes and **polymers**, and a **therapeutically effective amount of a compound capable of releasing nitric oxide** in an aqueous solution, particularly a nitric

oxide/nucleophile complex or derivative thereof. The pharmaceutical composition will generally contain an amount of the nitric oxide releasing compound sufficient to induce cytostasis or cytotoxicity among cells exposed to the pharmaceutical composition, and has particular utility in **antiparasitic, antifungal, and antibacterial treatments** (column 4, lines 38-48).

Green discloses that any biologically acceptable polymer can be used in his invention, including, for example, **polyethers, polyesters**, polyamides, peptides, **proteins**, oligonucleotides, and antibodies (column 10, lines 6-15).

Green discloses that the nitric oxide releasing compounds in the context of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation, which can be placed into pressurized acceptable propellants, including **nitrogen** (column 12, lines 33-37). Nitrogen is a buoyancy agent according to Applicant's own admission.

Green discloses the chemical formula of selected nitric oxide generators that can be used in his invention in Table 1 and **combinations thereof** may be used in Green's claimed formulations (column 14, lines 5-13).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5, 9, 16, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Nissen et al. (U.S. Patent No. US2002/0142964 A1).

Applicant's claims have been described *supra*.

Nissen discloses pharmaceutical compositions comprising **a polypeptide or polypeptide conjugate**, wherein said polypeptide or conjugate is a single chain multimeric polypeptide and polypeptide conjugate **exhibiting agonist activity**, comprising at least two monomeric units of a polypeptide of a type that is **biologically active** in monomeric form (see paragraphs 0022 and 0026). When said compositions also comprise are intended for use with a MDI they may also contain human serum **albumin**, one or more sugars or sugar alcohols (including **lactose** and **maltose**) a **hydrofluorocarbon**, and a surfactant (see paragraphs 0284-0285).

Albumin, lactose, maltose, polypeptides, and polypeptide conjugates are all encompassed by Applicant's definition of a polymer (state above). A hydrofluorocarbon is a buoyancy agent, per Applicant's own admission, and thus compositions comprising a hydrofluorocarbon are "controllably buoyant" as well. Tetrafluoroethane, a known hydrofluorocarbon, has a density (i.e. specific gravity) at 25 °C that is greater than 1.0063 g/cm^3 and hexafluropropane has a density at 0 °C greater than 1.0063 g/cm^3 (See e.g. CRC Handbook of Chemistry and Physics, p 3-306 and 3-306). Specific gravity is the ratio of the mass of a substance and the mass of an equal volume of water at 4 °C. Thus, one gram of tetrafluorethane would occupy a volume of approximately 0.8 ml and would have a specific gravity of approximately 1.25, because water has a density of approximately 1.0 g/ml at this temperature. Albumin is considered a hematological agent. In conclusion, Nissen meets the limitations of claims 1-3, 9, 16, and 20.

Claims 1-2, 6, 16, 17, 19, 20, 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Ouadji (U.S. Patent Application US2003/0138486).

Ouadji discloses dosage forms for improving the bioavailability of therapeutic agents that are metabolized in the upper gastrointestinal (GI) tract. The present invention improves the

bioavailability of by administering such therapeutic agents in a **floating dosage form** (paragraph 003).

Ouadji discloses a list of drugs known in the prior art that have been reported in floating dosage forms, including **aspirin**, ibuprofen, prednisolone, acetaminophen, **L-dopa**, etc. (paragraph 0010).

Ouadji discloses that the formulation comprises a therapeutic agent that is metabolized in with a controlled-release agent so as to be hydrodynamically balanced so that, in contact with gastric fluid, they have a **bulk density less than one g/ml** and therefore are **buoyant** in the gastric fluid (paragraph 0012).

Ouadji discloses that any dosage form known in the art (e.g. tablets, caplets, etc) may be used (paragraph 0022).

Ouadji discloses various optional **buoyancy agents**, used to maintain a relative density less than 1 g/ml, including **celluloses**, gums, **polysaccharides, starch, starch derivatives, and gelatin**. Optionally, the buoyancy agent may comprise sodium bicarbonate, sodium carbonate, calcium carbonate, lysine carbamate or any other agent **that produces carbon dioxide ($C0_2$) gas** when contacted with gastric acidity or an optional pharmaceutically acceptable acid such as, for example, citric acid or tartaric acid in the matrix can be used to increase buoyancy (paragraph 0024).

Ouadji discloses formulations **having a bulk density < 1 g/ml** comprising **ramipril** as the therapeutic agent (See Examples 1-9).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-31 rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (U.S. Patent No. 5,455,044) in view of Ouadji (U.S. Patent Application US2003/0138486).

Kim teaches a method for **treating a neurological disorder** using a slow-release vehicle for delivery of a **therapeutic agent** to the **cerebrospinal fluid (CSF)** of a human (column 1, lines 8-11).

Kim teaches that the surprising ability of the therapeutic agent **to ameliorate the neurological disorder** is due to the presentation of the therapeutic agent in a dispersion system, which **allows the agent to persist** in the cerebro-ventricular space (column 2, lines 34-36).

Kim defines a **neurological disorder** as any disorder that is present in the brain, spinal column, and related tissues, which are responsive to an appropriate therapeutic agent, including meninges and cell proliferative diseases (column 2, lines 42-48).

Kim teaches that the therapeutic agents used according to the method of the invention are administered to the CSF in a delivery system such as **synthetic or natural polymers** in the form of macromolecular complexes, nanocapsules, microspheres, etc., collectively known as dispersion systems. The particles comprising the system are about **20 nm-50 μm in diameter**. These dispersions may be administered intraventricularly, **intrathecally**, preferably by an injection of the particles by intralumbar puncture (column 3, lines 23-35).

Kim teaches that materials used in the dispersion are sterilizable including, albumin, **ethylcellulose, casein, gelatin**, and **soybean oil** (column 3, lines 37-40).

Kim teaches that the dispersion system density may be modified by **altering the specific gravity** to make the dispersion hyperbaric or hypobaric by addition of biocompatible molecules with high specific gravity (column 3, lines 43-49).

Kim teaches that in one class of dispersion the therapeutic agent is released from a polymer matrix made from synthetic polymers including, **polyesters**, polyurethanes,

polyorthoesters, and **polyanhydrides**. Regarding polyesters, **PLA and PLA/PGA polyesters** are cited as examples that have been extensively studied for use as polymer matrices of therapeutic agents. PLA, PGA, and PLA/PGA are poly(lactide), poly(glycolide), and poly(lactide-co-glycolide), respectively (column 3, lines 64-67 and column 4, lines 1-3).

Kim teaches the solid polymeric dispersion system can be produced initially as a larger mass, which is then ground, or otherwise processed, into particles small enough to maintain a dispersion in the appropriate physiologic buffer (column 4, lines 14-19).

Kim states that the term "**therapeutic agent**" as used for the compositions of the invention includes, without limitation, **drugs, radioisotopes**, and **immunomodulators**. The term "drugs" includes "non-proteinaceous" and "proteinaceous" drugs. "Non-proteinaceous" drugs include, for example, mitomycin C, daunorubicin, AZT, hormones, and 5-flurouracil. "Proteinaceous" drugs include **immunomodulators** and other biological responsive modifiers as well as **antibodies**, with an example being lymphokines (column 6, lines 9-11 and 23-53).

Kim teaches antibodies can also be used in **combination with other therapeutic agents** (column 7, lines 40-41).

Kim teaches that examples or **radioisotopes to treat cell proliferative disorders (i.e. radiopharmaceuticals)** include ^{125}I, ^{131}I, ^{90}Y, ^{67}Cu, ^{212}Bi, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, ^{188}Re (column 6, lines 54-67 and column 7, lines 1-3).

Kim teaches that the **exact dosages of therapeutic agents used will vary** depending upon such factors as the particular therapeutic agent and desirable medical effect, as well as patient factors such as age, sex, general condition and the like. Those of skill in the art can

readily take these factors into account and use them to establish effective therapeutic concentrations without resort to undue experimentation (column 8, lines 13-19).

Kim lacks the explicit teaching of compositions comprising a buoyancy agent and specific gravity values.

The teachings of Ouadji have been set forth above.

It would have been obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Kim and Ouadji, because both inventors teach dispersible pharmaceutical compositions comprising therapeutic agents and polymers, which have controlled-release or sustained-release properties. A skilled artisan would have been motivated to combine the teachings of Ouadji and Kim, to affect the density of Kim's formulations through the use of buoyancy agents, including formulations that would generate CO_2 gas *in situ* upon degradation of the polymer matrix (e.g. compositions comprising sodium bicarbonate and citric acid). It would have been obvious to a skilled artisan that one could lower a formulation's specific gravity by the inclusion of any pharmaceutically acceptable gas (e.g. O_2, N_2, Ar, He, Ne, or Xe) or mixture thereof (e.g. air is a mixture of N_2 and O_2) in said formulation, because it is well known that gases have much lower densities than either solids or liquids (see Brown, T. L. *Chemistry: The Central Science, 6th ed.* Prentice Hall: Englewood Cliffs, NJ, 1994, p 18). It also would have been obvious to a person of ordinary skill in the art to vary the specific gravity of biocompatible compositions through routine optimization practiced in the art. Regarding claim 12, it would have been obvious to a person of ordinary skill to use two different polymer particles, each containing a different therapeutic agent, because Kim teaches that antibodies (a proteinaceous drug) can be used in combination with other therapeutic agents. Modulating the

ratio of the quantities of the first and second polymeric particles is essentially modifying the dosages of the therapeutic agents contained within each particle. Claims 13-15 would have been obvious to a skilled artisan at the time of the instant invention, because the variation of different therapeutic agent dosages in a composition would have been achieved through the routine optimization of pharmaceutical formulations to adjust the therapy to the particular needs and symptoms of a patient.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (U.S. Patent No. 5,455,044) in view of Ouadji (U.S. Patent Application US2003/0138486) as applied to claims 1-10 and 12-31 above, and further in view of Chen et al. ("Inosine Induces Axonal Rewiring and Improves Behavioral Outcome After Stroke," *Proceedings of the National Academy of Science*, 2002, *99(13)*, 9031-9036).

Applicant's claim is drawn to a biocompatible composition comprising a therapeutic agent, a polymer, and a buoyancy agent, wherein the therapeutic agent is selected from the group consisting of inosine, citicholine, SOD, and dextrophan.

The teachings of Kim and Ouadji have been set forth above.

Kim and Ouadji lack the teaching of inosine as a therapeutic agent.

Chen teaches that the administration of **inosine** to rats with **unilateral cortical infarcts** (i.e. strokes) resulted in the stimulation of neurons on the undamaged side of the brain to extend new projections to denervated areas of the midbrain and spinal cord. This growth was paralleled by improved performance on several behavioral measures (abstract, last sentence).

Chen states that it is known in the art that inosine regulates the expression of multiple genes involved in axon growth, in at least some neurons, and in vivo inosine treatment can

promote extensive sprouting of the intact corticospinal tract (CST) into areas denervated by transecting the contralateral CST (p 9031, left hand column, 2nd paragraph).

Chen states "these studies show that inosine induces significant axonal reorganization in the rat brain after stroke and helps restore cortical control of the denervated forelimb" (page 9035, left hand column, 1st sentence in the Discussion).

Chen states that in animal models antioxidants, caspase inhibitors, glutamate receptor blockers, and other agents improve functional outcome after stroke by inhibiting cell death (p 9035, right hand column, last paragraph before the acknowledgements).

Chen concludes that inosine does not appear to exert neuroprotective effects, however because its effect on stimulating axonal rewiring are **complementary** to those of neuroprotective agents and inosine treatment **may represent a novel approach to improving function after stroke or CNS trauma** (p 9035, right hand column, last paragraph before the acknowledgements).

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Kim & Ouadji with those of Chen in a therapeutic composition intended for the treatment of a neurological disorder resulting from stroke or CNS trauma because inosine stimulates axonal rewiring, which is complementary to the effect of neuroprotective agents, such as antioxidants and glutamate receptor blockers, and the combined teachings of Kim & Ouadji teach dispersible pharmaceutical compositions with sustained release properties for the treatment of neurological disorders. A skilled artisan would have been motivated to use inosine, because its stimulatory effect on axonal growth has been demonstrated in rats, and thereby providing said

artisan with a reasonable expectation of success for the treatment of neurological disorders resulting from stroke or CNS trauma.

Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (U.S. Patent No. 5,455,044) in view of Ouadji (U.S. Patent Application US2003/0138486), in further view of Chen et al. ("Inosine Induces Axonal Rewiring and Improves Behavioral Outcome After Stroke," *Proceedings of the National Academy of Science*, 2002, *99(13)*, 9031-9036) as applied to claims 1-31 above, and further in view of Hatcher et al. (Society for Neuroscience, 19th Annual Meeting, Abstract #236.4, Oct. 23-28, 1999).

Applicant's claim is drawn to the composition of claim 12, wherein said first therapeutic agent is inosine and said second therapeutic agent is citicholine.

The teachings of Kim, Ouadji, and Chen have been set forth above.

The teachings of Kim, Ouadji, and Chen lack the teaching of a composition comprising inosine and citicholine as the therapeutic agents.

Hatcher teaches CDP-choline (also known as citicholine) significantly decreased neuronal death to 31±6% when ischemic duration was increased to 10 minutes and that two doses of citicholine (at 0 and 1 day) provided slight **neuroprotection** (abstract only)

It would have been obvious to a person of ordinary skill at the time of the instant invention to use inosine and citicholine in the same pharmaceutical compositions and said person would have been motivated to combine inosine and citicholine, because Chen teaches that inosine's effect on stimulating axonal rewiring are **complementary** to those of neuroprotective agents; Hatcher teaches citicholine has neuroprotective properties; and Chen suggests inosine treatment may represent a novel approach to improving function after stroke or CNS trauma. A

skilled artisan would have had a reasonable expectation of successfully combining inosine and citicholine to obtain a pharmaceutical composition appropriate for the treatment of neurological disorders for the above-mentioned reasons.

Other Matter

The Examiner respectfully suggests inserting a sentence in the Abstract describing the essential components of the claimed biocompatible composition, such as a therapeutic agent, a polymer, and a buoyancy agent. Claims 19 and 25 contain limitations that are considered sensitive matter (i.e. stem cells and fetal neural tissue) and may delay prosecution of this application. The Examiner respectfully suggests using a term's complete name in its first occurrence within the claims followed by its abbreviation in parentheses and the use of its abbreviation in subsequent claims (See claim 11, SOD; claim 19, NMDA; claim 21, ALS and TBI).

Conclusion

The drawings (Fig. 2), specification, and claims 19, 21, 25, and 28 are objected. Claims 1-33 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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James H. Alstrum-Acevedo, Ph. D.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER